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(71) Applicant and
(72) Inventor: **FISCH, Harry** [US/US]; 30 Springdale Road, Scarsdale, NY 10583 (US).

(74) Agent: **SCHAEFER, Ira, J.**; Clifford Chance Rogers & Wells LLP, 200 Park Avenue, New York, NY 10166-153 (US).

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/91744 A1

(54) Title: METHODS OF TREATING ANDROGEN DEFICIENCY IN MEN USING SELECTIVE ANTIESTROGENS

(57) Abstract: Male menopause is characterized by significant decreases in serum levels of bioavailable androgens. The administration of antiestrogens to men experiencing male menopause can remedy the relative androgen deficiency in men by stimulating the body's production of testosterone.

METHODS OF TREATING ANDROGEN DEFICIENCY IN MEN USING SELECTIVE ANTIESTROGENS

BACKGROUND OF THE INVENTION

The invention relates to the new use of antiestrogens for the production of a pharmaceutical agent for treating a relative androgen deficiency in men.

In men, increasing age leads to a reduction of testicular androgen production and androgen concentration in the organism. In contrast to the situation in women, in whom estrogen production drops to castration values within a comparatively short period, this takes decades in men and involves a gradual drop. The total concentration of testosterone in the serum in the older age group is significantly reduced compared to the values in young men. Because of the increase in steroid hormone-binding globulin (SHBG) that coincides with the aging process, moreover, the proportion of free, unbound, and thus biologically active testosterone drops. In addition, the serum levels of estrogens, although they are produced from androgens by direct conversion, do not drop in the same way as a function of age. As a result, the hormonal environment is significantly altered.

In men, the hormonal environment of the sexual steroids is characterized by a significant preponderance of

androgens over estrogens. While the circulating main component of androgens, testosterone, is detected in the serum in units in the range of nmol/l, the estrogen antagonist, estradiol, can be measured only in the range of pmol/l. This considerable preponderance of androgen can be detected basically in the entire late puberty period of life, but there is a clearly different intensity of this androgen dominance as a function of age. With increasing age and particularly so in those over the age of 60, there is a less pronounced emphasis of the androgen preponderance.

In older men there are relative decreases in the preponderance of testosterone by 30-50% compared to the previous values found in young men.

The relative testosterone deficiency per se can be regarded as responsible for a number of age-related disorders. Reduction of muscle mass accompanied by limitation of body performance capacity, reduction of bone density and in individual cases even osteoporosis, an increase in prostate size referred to as benign prostatic hyperplasia, reduction of libido and potency, and psycho-vegetative disorders such as depression, which are disorders that are often generically referred to as Male Menopause and are caused by relative androgen deficiency in men. Libido is the desire to obtain an erection, while potency is the ability to have that erection.

It is known that in younger men, testosterone values are also effectively increased by daily treatment with

antiestrogens to treat male infertility. Treatment of Male Infertility, Springer-Verlag Berlin, Heidelberg, New York 1982; Fuse, H. et al., Archives of Andrology 31 (1993) 139-145); Nonsurgical Treatment of Male Infertility, Jarow, J., Infertility in the Male, pp. 410-422. However, it has been thought that antiestrogens do not seem well suited for treatment of a relative androgen deficiency in men. Thus, for example, U.S. patent 5,861,389 proposes the use of at least one aromatase inhibitor for the production of a pharmaceutical agent for treating a relative androgen deficiency in men.

SUMMARY OF THE INVENTION

The object of the present invention is to treat a relative androgen deficiency in older men and/or the specific disorders related to male menopause by the use of antiestrogens.

It has been noted that the use of antiestrogens in treating a relative androgen deficiency in older men results surprisingly in a long-term increase in the androgen level.

By gradually stimulating the body to produce testosterone, the antiestrogens result in an endogenic rebalancing of the testosterone/estrogen ratio in men. As a result, the relative androgen deficiency is compensated for.

For the purposes of this invention, antiestrogens are all those compounds that compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of

intracellular estrogen receptors. As antiestrogens, therefore, all such compounds are suitable, such as, for example:

tamoxifen citrate which is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1) and sold under the trademark Novladex; and

clomiphene citrate which is 2[p-(2- chloro-1,2-diphenylvinyl) phenoxy]] trieth lamine citrate (1:1). It has the molecular formula of C26H28ClNO•C6H8O7 and a molecular weight of 598.09 and is sold under the trademark Clomid.

The list of antiestrogens above is not exhaustive, other compounds that meet the set requirements, are also considered.

A pharmaceutically effective dosage of the antiestrogen is administered in older men for an effective time period, preferably continuously. For example, at a daily dose of 5-10 mg once or twice a day, tamoxifen is administered to obtain a target range of mid-normal testosterone levels. A dose of 10-25 mg of clomid daily or every other day and up to 100 mg is administered to obtain the mid-normal levels. Measuring the serum concentration of testosterone and estradiol can thus give early indication of whether the desired hormone balance was achieved and optionally whether dose adjustment can be undertaken.

In general, 5 to 1000 mg, preferably 10 to 100 mg, of antiestrogen clomiphene citrate or tamoxifen citrate or a biologically equieffective amount of another antiestrogen is used daily or every other day to treat a relative androgen deficiency in men.

The antiestrogens can be administered, e.g., orally, parenterally or transdermally by a patch for example.

For the preferred oral administration, suitable means are especially tablets, coated tablets, capsules, pills, suspensions, or solutions that can be produced in a way that is commonly used and familiar to one skilled in the art, with the additives and vehicles that are commonly used for the formulation of antiestrogens that are to be administered orally.

The pharmaceutical agent that is produced according to the invention contains as an active ingredient per dosage unit of the antiestrogen at a daily or every other day dosage of 5 to 100 mg in addition to the commonly used additives, vehicles and/or diluents or other antiestrogens at biologically equieffective dosages.

When antiestrogens are used for treating male menopause, the estrogen concentration is effectively lowered. The easy controllability of the treatment distinguishes treatment with an antiestrogen. For 10 mg tablets, each tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen. For 20 mg tablets, each

tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen. The inactive ingredients are carboxymethylcellulose calcium, magnesium stearate, mannitol and starch.

Clomiphene citrate tablets is a mixture of two geometric isomers [cis (zuclomiphene) and trans (enclomiphene)]containing between 30% and 50% of the cis-isomer. A standard commercially available tablet contains 50 mg clomiphene citrate and the following inactive ingredients: corn starch, lactose, magnesium stearate, pregelatinized corn starch, and sucrose. The current tablets are used primarily for treating female infertility. Treatment according to the present invention contemplates a redosing to accommodate the lower dosages specified herein.

It is also contemplated that combinations of antiestrogens can be administered or that combinations of antiestrogens and other testosterone producing drugs can be used.

What is claimed is:

1. A method of treating androgen deficiency in men comprising administering a selective antiestrogen.

2. The method according to claim 1, wherein the selective antiestrogen is clomiphene.

3. The method according to claim 1, wherein the selective antiestrogen is clomiphene citrate.

4. A method of treating disorders related to male menopause in men comprising administering an antiestrogen.

5. The method according to claim 4, wherein the disorder is reduction of muscle mass.

6. The method according to claim 4, wherein the disorder is limitation of body performance capacity.

7. The method according to claim 4, wherein the disorder is reduction of bone density.

8. The method according to claim 4, wherein the disorder is reduction of libido.

9. The method according to claim 4, wherein the disorder is reduction of potency.

10. The method according to claim 4, wherein the disorder is reduction of benign prostatic hyperplasia.

11. The method according to claim 1, wherein the selective antiestrogen is tamoxifen.

12. The method according to claim 1, wherein the selective antiestrogen is tamoxifen citrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/15900

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/225, 31/135
US CL :514/648, 651

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/648, 651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,728,688 A (LABRIE) 17 March 1998 (17.03.98), see the entire document.	1-12
A	US 5,861,389 A (RADLMAIER et al.) 19 January 1999 (19.01.99), see the entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 JULY 2001	Date of mailing of the international search report 05 NOV 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAYMOND J. HENLEY III Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998) ★

09/980658

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 April 2002 (08.04.02)	
International application No. PCT/US01/15900	**Applicant's or agent's file reference** 7202-221
International filing date (day/month/year) 15 May 2001 (15.05.01)	**Priority date** (day/month/year) 26 May 2000 (26.05.00)
Applicant FISCH, Harry	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 December 2001 (11.12.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Odile ALIU
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: IRA J. SCHAEFER
CLIFFORD CHANCE ROGERS & WELLS LLP
200 PARK AVENUE
NEW YORK, NY 10166-0153

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 7202-221	Date of Mailing *(day/month/year)* 05 NOV 2001
International application No. PCT/US01/15900	FOR FURTHER ACTION **See paragraphs 1 and 4 below**
Applicant HARRY FISCH	International filing date *(day/month/year)* 15 MAY 2001

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later) .

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer RAYMOND J. HENLEY III
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

(See notes on accompanying sheet)